Design and Preparation of Medicinally Relevant Dihydropyridine Derivatives

SYNOPSIS

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Faculty of Sciences

UNIVERSITY DEPARTMENT OF CHEMISTRY

B. N. MANDAL UNIVERSITY, MADHEPURA

FOR THE DEGREE OF

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BY

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B.N.MANDAL UNIVERSITY, LALOO NAGAR, MADHEPURA

SYNOPSIS OF RESEARCH WORK FOR Ph.D. DEGREE IN THE FACULTY OF SCIENCE (CHEMISTRY)

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Design and Preparation of Medicinally Relevant Dihydropyridine Derivatives

(i) Work Plan

a. Purpose and need of the study

Heterocyclic compounds form the structural backbone of numerous biologically active molecules and play an essential role in medicinal chemistry. Among these, nitrogen-containing six-membered rings, especially pyridines and their reduced forms, dihydropyridines, are widely recognized as privileged scaffolds due to their broad pharmacological relevance. Dihydropyridines occupy a unique biological position because they participate directly in vital redox processes. In living systems, the pyridine ring of nicotinamide adenine dinucleotide (NAD^+) is reduced to its dihydropyridine form (NADH), facilitating key metabolic transformations. A similar process occurs in the $NADP^+$/NADPH system, further emphasizing the biochemical importance of this ring system.

Their relevance extends to pharmaceuticals as well. Analysis of FDA-approved N-heterocyclic drugs shows that nearly 18% contain pyridine or dihydropyridine units, with therapeutic applications spanning oncology, infectious diseases, inflammatory disorders, and neurological conditions. Owing to this wide spectrum of activities, dihydropyridines have become central to modern drug design. They display diverse pharmacological properties such as antitumor, antimicrobial, anti-inflammatory, anticonvulsant, antimalarial, and antihypertensive activities. Their structural adaptability and ability to engage in multiple

biological interactions make them valuable targets for synthetic development.

Given their broad therapeutic potential and the continuing demand for new bioactive molecules, the proposed research aims to develop efficient and sustainable methodologies for synthesizing medicinally important dihydropyridine derivatives. The synthesized compounds will then be evaluated for relevant biological activities.

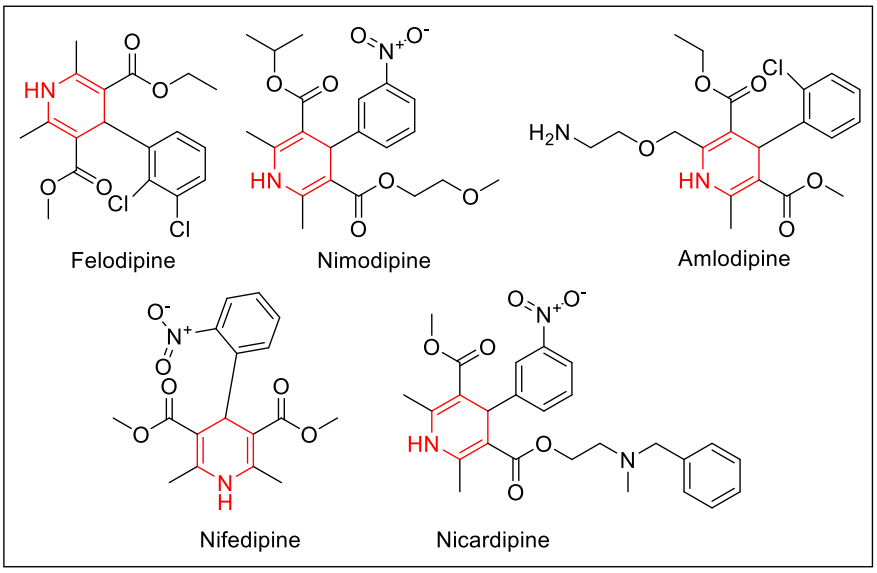


Figure 1) Structures of biologically active dihydropyridines.

Review of Literature of proposed work

The dihydropyridine framework represents one of the most extensively studied heterocyclic systems in medicinal and natural product chemistry. Many naturally occurring alkaloids incorporate this core, and enzymatic redox processes, such as the conversion of NAD^+ to NADH and $NADP^+$ to NADPH, highlight its indispensable biological role. Pyridine- and dihydropyridine-based molecules are significantly represented in FDA-approved drugs, accounting for about one-fifth of nitrogen-containing heterocyclic pharmaceuticals. These compounds exhibit therapeutic potential in diverse disease areas including cardiovascular disorders, infections, inflammation, cancer, and neurological conditions.

Dihydropyridines are best known for their role as calcium-channel blockers in antihypertensive therapy, with drugs such as amlodipine, nifedipine, felodipine, azelnidipine, clevidipine, and nilvadipine forming the core of this class. Several exhibit additional clinical applications, for example, nifedipine in Raynaud's syndrome and prevention of preterm labor. Natural dihydropyridines like huperzine serve as potent acetylcholinesterase inhibitors, and compounds such as ciclopirox are widely used antifungals. Drugs like milrinone and amrinone, containing both pyridine and dihydropyridine motifs, are clinically important vasodilators.

Because of this broad utility, significant research has focused on developing efficient synthetic strategies. Numerous catalytic systems, including $Zr(HPO_4)_2$, CECIL-supported ionic liquids, Fe_3O_4 nanoparticles, MNP@BSAT@$Cu(OAc)_2$, and various nanostructured catalysts, have been optimized to improve yield, selectivity, and environmental compatibility in the synthesis of dihydropyridine and related quinoline derivatives via Hantzsch-type reactions.

b. Details of the project with chapterization

Chapter- I: Introduction
Chapter- II: Survey of previous works
Chapter- III : Experimental
Chapter- IV: Result and Discussion
Chapter- V : Conclusion

Chapter I: Introduction

This chapter will introduce heterocyclic chemistry with emphasis on the importance of dihydropyridines as privileged scaffolds. It will discuss their natural occurrence, biochemical redox functions, pharmaceutical relevance, and the rationale for choosing dihydropyridine derivatives as the focus of the present work.

Chapter II: Survey of Previous Works

A comprehensive review of published literature on the synthesis, structural diversity, catalytic methods, and biological activities of dihydropyridine derivatives will be provided. Special attention will be given to multicomponent reactions and heterogeneous catalysts. Research gaps and areas requiring further investigation will be identified.

Chapter III: Experimental

This chapter will detail the materials, reagents, catalysts, and experimental conditions used in the synthesis of the target compounds. It will describe reaction procedures, optimization steps, purification methods, and analytical characterization techniques such as NMR, IR, UV–Vis, and mass spectrometry.

Chapter IV: Results and Discussion

Experimental data, reaction outcomes, spectral characterization, and structural confirmations will be presented and discussed. Trends in reactivity, yields, and substituent effects will be analyzed. Biological evaluation results will be included, along with structure–activity relationship (SAR) discussions.

Chapter V: Conclusion

The concluding chapter will summarize the achievements of the research, highlighting the efficiency of the developed synthetic methods and the biological potential of the synthesized derivatives. Possible future directions and applications will also be suggested.

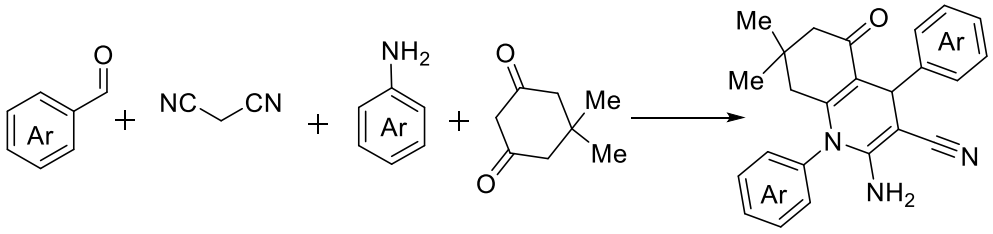
c. **Hypothesis**

It is hypothesized that structurally modified dihydropyridine derivatives synthesized through optimized and sustainable methodologies will exhibit improved biological activity. The introduction of suitable substituents or fused heterocyclic units is expected to modulate electronic and steric properties, thereby enhancing the pharmacological profile. Additionally, the use of efficient catalysts and green synthetic conditions should yield compounds with superior purity, stability, and functional diversity. Based on the established therapeutic

importance of dihydropyridines, the newly synthesized derivatives are anticipated to serve as promising leads for further drug development.

D. Methodology

The proposed research will focus on developing an efficient, eco-friendly, and high-yielding synthetic route for dihydropyridine derivatives. A systematic optimization study will be conducted using a newly selected catalytic system. A one-pot, four-component Hantzsch-type reaction involving an aldehyde, malononitrile, dimedone, and aniline will be used as the model reaction (Scheme 1). Parameters such as catalyst type and loading, solvent, temperature, and reaction time will be examined to achieve maximum yield under green and economical conditions. After establishing optimal conditions, the substrate scope will be explored by synthesizing a series of dihydropyridine derivatives. All products will be purified and characterized using standard analytical techniques, and selected derivatives will be subjected to biological evaluation to determine their pharmacological potential.



Scheme 1: Synthesis of hetrocyclic dihydropyridine derivatives.

e. Bibliography

(1) Singh, V.; Rajput, K.; Singh, S.; Srivastava, V. Montmorillonite K-10 Catalyzed Synthesis of Hantzsch Dihydropyridine Derivatives from Methyl Arenes via in Situ Generated Ammonia under Microwave Irradiation in Neat Conditions. *RSC Adv.* **2024**, *14* (37), 27086–27091. https://doi.org/10.1039/D4RA04990J.

(2) Hu, X.; Chen, L.; Li, H.; Xu, Q.; Liu, X.; Feng, X. Enantioselective Catalytic Hantzsch Dihydropyridine Synthesis. *ACS Catal.* **2023**, *13* (10), 6675–6682. https://doi.org/10.1021/acscatal.2c05888.

(3) Lavanya, G.; Abdul Khadar Iynoon Jariya, S. bee; Sasikala, M.; Kalpana, V.; Padmanaban, A.; Wang, J.; Ali, B. M. Recent Advances in the Synthesis of

Dihydropyridine and Their Corresponding Fused Systems via Multi-Component Hantzsch Reaction Using Catalytic Nanomaterials. *ChemistrySelect* **2024**, *9* (43). https://doi.org/10.1002/slct.202403664.

(4) Faizan, M.; Kumar, R.; Mazumder, A.; Salahuddin; Kukreti, N.; Tyagi, P. K.; Kapoor, B. Hantzsch Reaction: The Important Key for Pyridine/Dihydropyridine Synthesis. *Synth. Commun.* **2024**, *54* (15), 1221–1244. https://doi.org/10.1080/00397911.2024.2377738.

(5) Sonali Anantha, I. S.; Kerru, N.; Maddila, S.; Jonnalagadda, S. B. Recent Progresses in the Multicomponent Synthesis of Dihydropyridines by Applying Sustainable Catalysts Under Green Conditions. *Front. Chem.* **2021**, *9*. https://doi.org/10.3389/fchem.2021.800236.

(6) Bosica, G.; Abdilla, R. Novel Biopolymer-Based Catalyst for the Multicomponent Synthesis of N -Aryl-4-Aryl-Substituted Dihydropyridines Derived from Simple and Complex Anilines. **2024**.

(7) Ling, Y.; Liu, Y. The Expanding Role of Pyridine and Dihydropyridine Scaffolds in Drug Design. **2021**, No. October.

(8) Ebrahimipour, S. Y.; Abaszadeh, M.; Castro, J.; Seifi, M. Synthesis , X-Ray Crystal Structure , DFT Calculation and Catalytic Activity of Two New Oxido-Vanadium (V) Complexes Containing ONO Tridentate Schiff Bases. *Polyhedron* **2014**, *79*, 138–150. https://doi.org/10.1016/j.poly.2014.04.069.

(9) Abaszadeh, M.; Seifi, M. Crown Ether Complex Cation Ionic Liquids : Synthesis and Catalytic Applications for the Synthesis of Tetrahydro-4 H -Chromene and 1 , 4-Dihydropyridine Derivatives. **2017**, *5993*. https://doi.org/10.1080/17415993.2017.1293058.

(10) Abaszadeh, M.; Seifi, M.; Asadipour, A. Erratum to : Ultrasound Promotes One-Pot Synthesis. *Res. Chem. Intermed.* **2015**, 11164. https://doi.org/10.1007/s11164-014-1711-9.

(11) Sanaei, S.; Hakimeh, R.; Boshra, S.; Eshkevari, M. Onto the Metal – Organic Framework MIL - 101 (Cr) as a Superior and Reusable Heterogeneous Catalyst for the Preparation of Hexahydroquinolines. *Res. Chem. Intermed.* **2021**, *47* (5), 2143–2159. https://doi.org/10.1007/s11164-020-04390-7.

(12) Mazloumi, M.; Shirini, F. One-Pot Four-Component Synthesis of N-Aryl-1,8-dioxo-decahydroacridines, N-Arylquinolines and Spiro[Indoline-3,4′-Quinolines] Catalyzed by a New Ionic Liquid Immobilized on Nonporous SiO2. *Res. Chem. Intermed.* **2022**, *48* (12), 5113–5131. https://doi.org/10.1007/s11164-022-04851-1.

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